

### **REMARKS**

Claims 1-11, 14, 18, 20-28, 30 and 33 have been canceled, claims 12, 13, 15-17, 19, 29, and 31 have been amended, and claims 34-62 have been added. The amendments to the claims, and the added claims, are fully supported by the original claims and the specification. Claims 12, 13, 15-17, 19, 29, 31, 32 and 34-62, including independent claims 34, 44, and 55, are therefore presented for examination and reconsideration which is respectfully requested in view of the foregoing amendments and following remarks.

In the June 13, 2007, Office Action, claims 11-16 and 21-23 were rejected under 35 USC 102(b) as anticipated by Crooke, and claims 11-23, 25-27, 29 and 31-33 were rejected under 35 U.S.C. § 103(a) as obvious over McSwiggen in view of Holen. The specific grounds for rejection, and applicants' response thereto, are set forth in detail below.

#### **Support for amendments**

Added claim 34 is based on original claim 11, and is further supported at page 12, lines 4-5, page 25, lines 2-3 and by figures 12, 15, and 16. Claim 44 is supported at page 12, lines 4-5, page 22, lines 28-30 and 34, page 23, lines 7-10, and page 24 of the specification. Claim 55 is supported at page 25, lines 4-13, and particularly at page 23, line 10. Claims 51-53 and 60-62 are supported at page 25, lines 21 *et seq.*

#### **Rejection Under 35 U.S.C. §102(b)**

Claims 11-16 and 21-23 are rejected as anticipated by Crooke. Applicants respectfully traverse.

It is axiomatic that, for a prior art reference to be anticipatory, every element of the claimed invention must be identically shown in a single reference. In re Bond, 15 USPQ2d 1566 (Fed. Cir. 1990). Applicants traverse each anticipation rejection, since Crooke fails to teach every element of the rejected claims.

Crooke merely describes a conventional "gapmer" antisense molecule that serves as a substrate for RNaseH. Thus, each strand contains a sequence of 8 unmodified ribonucleotides flanked on each side by a sequence of modified ribonucleotides. The Examiner asserts that this arrangement creates a "pattern." Applicants respectfully submit that Crooke fails to describe anything that one skilled in the art would recognize as a pattern. In any event, it is clear that

Crooke fails to describe either a sequence of alternating 2'-modified and unmodified nucleotides linked by a phosphodiester bond as required by instant independent claim 34 or stretches containing an alternating pattern of groups of 2'-modified nucleotides linked by a single unmodified nucleotide as defined in independent claim 44. Similarly, Crooke fails to describe stretches having the alternating pattern of modification MOMOMOMOM, where M and O are respectively 2'-modified and non-modified nucleotides, as recited in claim independent 55.

Accordingly, Crooke fails to teach each and every element of the instant claims and applicants respectfully request withdrawal of the rejection.

### **Rejections Under 35 U.S.C. §103(a)**

Claims 11-23, 25-27, 29 and 31-33 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over McSwiggen et al. in view of Holen et al. Specifically, the Examiner asserts that Figure 5B of McSwiggen describes a sequence containing a modified nucleotide “that is repeated at least once forming a pattern wherein the pattern is, starting from the 5' end: two 2'-position modified nucleotides i.e. groups, wherein this pattern of modified groups is flanked by an unmodified nucleotide on each side.” Applicants respectfully traverse.

McSwiggen describes double stranded ribonucleic acid molecules that are modified in a manner that allegedly enhances stability. Specifically, McSwiggen states that:

all pyrimidine nucleotides that may be present are 2'-O-methyl modified nucleotides except for (N N) nucleotides, which can comprise naturally occurring ribonucleotides, deoxynucleotides, universal bases, or other chemical modifications described herein.

See McSwiggen, paragraph 0146. (N.N) nucleotides apparently are unpaired nucleotides in the single-stranded overhangs of the ribonucleic acids. It is not clear why the molecule shown in Figure 5B, as cited by the Examiner, does not follow the modification pattern specified elsewhere in McSwiggen, and it seems likely that the sequence of Figure 5B contains a typographical error. This is particularly the case where the description of Figure 5 (see paragraph 0147) states that Figures 5A-F “applies [sic] the chemical modification described in FIGS. 4A-F.” The modification describes in FIGS 4A-F requires modification of all internal pyrimidine nucleotides. Nevertheless, whether or not Figure 5B contains a typographical error, it neither teaches nor suggests the instantly claimed ribonucleic acid molecules.

Specifically, McSwiggen fails to teach or suggest a double stranded ribonucleic molecule where each strand contains a sequence of alternating 2'-modified and unmodified nucleotides linked by a phosphodiester bond as required by instant independent claim 34, or stretches containing an alternating pattern of groups of 2'-modified nucleotides linked by a single unmodified nucleotide as defined in independent claim 44. Similarly, McSwiggen fails to teach or suggest stretches having the alternating pattern of modification MOMOMOMOM, where M and O are respectively 2'-modified and non-modified nucleotides, as recited in claim independent 55. To the extent that the system of making modifications described by McSwiggen generates anything that could be considered a "pattern" it does so purely as a result of chance because of the sequence of the target nucleotide and the resulting arrangement of pyrimidines. A chance occurrence could not teach or suggest to one of ordinary skill in the art the instantly claimed molecules that contain a repeating pattern of modified and unmodified nucleotides, regardless of sequence.

More particularly, the specific arrangements of modified and unmodified nucleotides described by McSwiggen are quite distinct from the arrangements set forth in the instant claims. The only sequence in McSwiggen cited by the Examiner as showing anything resembling a "pattern" has the following arrangement of modified and unmodified nucleotides:

in the sense strand:                    5'-MuMuuMMuMMuMMuMuuMMuu-3'

and in the antisense strand:    3'-uuuMuMMuuMuMuuuuMuMuu-5'

where M is a modified nucleotide and u is an unmodified nucleotide. The portion of the McSwiggen sequence alleged by the Examiner to show a "pattern" has 6 nucleotides arranged in the fashion MMuMMu (see page 4, first paragraph, of the Office Action). To the extent that one of ordinary skill in the art would understand that this arrangement constitutes a "pattern," the pattern does not extend to an alternating stretch of 15 or more alternating modified and unmodified nucleotides as recited in claim 34. Moreover, McSwiggen's molecule has an antisense strand that contains two and three-nucleotide sequences of unmodified nucleotides, in contrast to the molecules recited in claims 34, 44 and 55 where both strands have a pattern containing single unmodified nucleotides. Indeed, the antisense strand in McSwiggen does not contain anything that could be considered to show a repeating pattern of groups of modified nucleotides. Holen fails to remedy any of these deficiencies.

For at least these reasons, the cited art fails to teach, suggest or disclose all the limitations of the claims. Accordingly, a *prima facie* case of obviousness has not been established by the Examiner, and withdrawal of the rejection respectfully is requested.

## **CONCLUSION**

In view of the foregoing amendments and remarks, applicants respectfully submit that the application is in condition for allowance. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned to expedite prosecution of the application.

The Commissioner is hereby authorized by this paper to charge any fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-3840. **This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).**

Respectfully submitted,



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Paul M. Booth  
Attorney for Applicant  
Reg. No.: 40,244

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**Proskauer Rose LLP**  
1001 Pennsylvania Avenue, NW  
Suite 400  
Washington, DC 20004  
Telephone: 202.416.6800  
Facsimile: 202.416.6899  
CUSTOMER NO: 61263

Customer No. 61263